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EDITORIAL COMMENT

Molecular Remodeling in Human Heart Failure*

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The past decade has seen an explosion of research into the pathogenesis of cardiac hypertrophy and remodeling (1). At the cellular level, remodeling can be regarded, in large part, as the response of cardiac myocytes to biomechanical stress. Stressors such as pressure or volume load, reactive oxygen species, cytokines, and circulating neurohormones activate a complex network of signaling pathways within cardiac myocytes. These pathways converge on a core set of cardiac transcription factors, co-regulators, and as shown recently, micro ribonucleic acids (2,3) to alter cardiac gene expression and induce myocyte hypertrophy and dysfunction. These changes are similar to those observed during fetal cardiac development, and the process of hypertrophy is often described as reactivation of a "fetal gene program." Although many changes occur, the most well-characterized include a shift in expression of contractile isoforms, increased expression of natriuretic peptides, and alterations in expression of calcium cycling genes. Hence, animal models have shown that gross chamber remodeling is accompanied by a characteristic "molecular remodeling" believed to play a causative role in the pathogenesis of heart failure.

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Translating these findings to human subjects has been challenging. To study molecular aspects of human heart failure, investigators have capitalized on situations in which myocardium can be conveniently obtained with minimal patient risk, such as at the time of cardiac transplantation (4,5) or placement of ventricular assist devices (6–9). These studies have determined that molecular remodeling does occur in human heart failure in a manner that parallels findings in animal models. Work from our own group has demonstrated that many of the same hypertrophic transcription factors identified in murine models might mediate this process (5). Importantly, heart failure therapies that lead to clinical improvement reverse the molecular changes observed in heart failure, so that expression of the fetal cardiac gene program fades as ventricular function improves. This has been demonstrated in human subjects with serial assessments of cardiac gene expression before and after treatment with beta-blockers (10) and before and after mechanical unloading with ventricular assist devices (6–9).

In this issue of the *Journal*, Vanderheyden et al. (11) demonstrate that, like beta-blockers and ventricular assist devices, cardiac resynchronization therapy also causes "reverse molecular remodeling." The authors performed left ventricular endomyocardial biopsies in a small cohort of stable heart failure patients undergoing elective implantation of biventricular pacing devices and repeated these biopsies after 4 months of cardiac resynchronization. Compared with control subjects with normal ventricular function, heart failure patients at baseline showed decreased expression of alpha-myosin heavy chain (α-MHC), β-MHC, sarcoplasmic-endoplasmic reticulum calcium ATPase 2-a (SERCA2a), and phospholamban and increased expression of brain natriuretic peptide (BNP), all of which are typical features of heart failure in humans. After 4 months of resynchronization therapy, patients who showed improvement in ventricular function and reduction in heart failure symptoms also showed restoration of cardiac gene expression toward a more normal pattern, with an increase in expression of α-MHC and SERCA2a and a decrease in BNP. By contrast, patients who showed no clinical response showed no change in molecular profile after resynchronization therapy. Hence, clinical response was associated with reverse molecular remodeling and a "tuning down" of the fetal gene program.

The major strengths of this study are the focus on highly relevant molecular markers of heart failure, the use of repeated measures in the same patients to reduce variability, and the assessment of gene expression in the left ventricle, the chamber of interest, as opposed to biopsies of the right ventricular septum. It was not feasible, like many studies involving endomyocardial biopsy, to study a large population, and the small sample size and small amount of available tissue are the major study limitations. As a result, the authors were underpowered to determine whether gene expression changes differed depending on the underlying etiology of heart failure, which has been suggested by previous studies (4). In addition, assessing a larger number of genes with more comprehensive strategies, such as whole-genome expression profiling, was also not feasible. That said, the overall study findings are highly compelling when viewed in the larger context of published data and they have since been verified by an independent group with similar approaches (12).

Thus, highly effective heart failure therapies, including neurohormonal blockade, mechanical unloading, and now cardiac resynchronization, improve cardiac function in association with reverse molecular remodeling. These consistent findings have several clinical implications. First, they

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suggest that molecular markers that track the fetal gene program could serve as clinically useful biomarkers of heart failure progression. Circulating BNP has already become a standard in this area, but it seems likely that expanded panels of biomarkers could be even more informative. Developing these "molecular signatures" will require studies in large clinical cohorts that demonstrate their ability to predict future clinical events and to predict response to specific heart failure therapies. In addition, obtaining the molecular signature must be convenient enough to repeat over time, which is currently not the case for gene expression signatures obtained via endomyocardial biopsy.

Second, because cardiac gene expression seems to be a final common mediator of heart failure, it should be tested as a direct therapeutic target. Several strategies are evolving to accomplish this, including the use of histone deacetylase inhibitors (13) and short hairpin ribonucleic acid (14) to alter expression of endogenous myocardial genes and the use of adenoviral vectors to introduce exogenous genes to improve cardiac function. For example, the ongoing CUPID (Safety Study of Gene Transfer Agent MYDICAR [AAV1/SERCA2a] to Treat Heart Failure) clinical trial (15) is currently testing the safety and early efficacy of an intracoronary SERCA2a transgene as a strategy to improve cardiac function in chronic heart failure (16). This trial will provide some of the first human data testing molecular therapy for heart failure.

Finally, the logistical challenges of studying human cardiac gene expression emphasize the need for newer noninvasive approaches to study molecular aspects of cardiac remodeling in human subjects. Many strategies are evolving to do this, including novel circulating biomarkers, studies of inherited gene variation in hypertrophic signaling pathways, and molecular imaging. These techniques will undoubtedly help us test the clinical relevance of mechanisms of cardiac remodeling discovered in animal models and thereby identify novel therapeutic targets for human heart failure.

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